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DATE: July 7, 2005

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION AND EXPOSURE ASSESMENT DOCUMENTS FOR THE ACTIVE INGREDIENT CARBOFURAN

Thank you for the opportunity to review the draft risk characterization (RCD) and exposure assessment (EAD) documents for carbofuran, both dated March 1, 2005, prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code (HSC), Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the TAC documents. As part of its statutory

responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

This draft RCD (in conjunction with the accompanying EAD) evaluates occupational, dietary and airborne (ambient and application site) exposures to carbofuran. Because exposures of the general public to carbofuran in ambient and application site air were evaluated in this RCD package, OEHHA considers this active ingredient a candidate TAC. Overall, we find both documents thorough and clearly written. Generally, we find the assumptions, considerations and conclusions contained in these documents appropriate, scientifically defensible and sufficiently supported. OEHHA does have a major concern, however, regarding the setting of the seasonal and chronic regulatory levels one order-of-magnitude higher than the critical acute LED_{05}. This concern and other suggestions and recommendations are outlined below. We hope that you find our comments and recommendations supportive and useful.

Carbofuran is a broad spectrum, systemic insecticide, acaricide and nematicide that is effective versus a large number of pests in many crops. It is a carbamate and a potent cholinesterase inhibitor, an effect responsible for its usefulness a pesticide and its acute toxicity to humans and other non-target species. Due to a number of unintentional bird-kill incidents in the late 1980s and early 1990s, granular formulations of carbofuran are banned in California. Currently there is only one product (Furdan 4F, a 44% liquid concentrate) registered for use in California.

Our comments on the draft RCD (and EAD where applicable) are as follows:

1. Acute oral, dermal and inhalation exposures to carbofuran are evaluated in the draft RCD using the results from a developmental toxicity range finding study in rats (WARF, 1978). From this study, a maternal lowest-observed-adverse effect level (LOAEL) of 0.1 mg/kg is identified based on chewing behavior observed at this and higher (0.3 and 1.0 mg/kg gavage doses) doses. No reproductive or developmental effects were observed in the study. The chewing behavior observed in the study exhibited a dose-related increase in incidence was considered an acute response to treatment. Benchmark dose (BMD) analysis of the dataset derived an LED_{05} (lower bound on the 5% BMD response) of 0.01 mg/kg that was used to evaluate risk in the RCD.

   The use of chewing behavior with a LED_{05} of 0.01 mg/kg as a critical endpoint and regulatory value is supported by the results of the Jayatunga et al. (1998) study from which a LED_{05} of 0.01 mg/kg based on decreased locomotor activity and head-dip behavior at all doses tested was also derived using BMD (observed LOAEL of 0.2 mg/kg). Additional justification and support for using the LED_{05} of 0.01 mg/kg from the WARF (1978) study is provided by the results of a human oral exposure study (FMC, 1976) showing cholinergic signs of dry mouth, salivation, diaphoresis, abdominal pain,

drowsiness, nausea, and vomiting at a dose level of 0.25 mg/kg – a dose only 2.5 times greater than the LOAEL of 0.1 mg/kg in the critical rat study. It is noted in the RCD that the critical endpoint of chewing behavior is not unprecedented, in that this behavior is a critical acute determinant in several risk assessments (acephate, fenthion, azinphosmethyl, and mepivinphos) and is a critical subchronic determinant in one case (dichlorvos), albeit in these examples chewing behavior was accompanied by other cholinergic signs at the same dose. A case is made (in the RCD) that this chewing behavior is an *adverse* effect that is potentially central nervous system in origin. Indeed, on page 125 of the RCD, the following statement is found: "Yet the distinct possibility of central nervous system involvement, with the attendant possibility that other centrally coordinated, but difficult-to-document, processes such as learning or perception were also affected, suggested the possibility that the effect was more severe." Based on the evidence provided in the RCD, OEHHA agrees with the identification of 0.01 mg/kg as the acute regulatory value for carbofuran.

Seasonal (oral, inhalation and dermal) and chronic (oral) exposures to carbofuran are evaluated in the RCD based on a NOAEL of 0.1 mg/kg-day identified in the rat oral (gavage) reproduction study by Pant et al. (1995). The NOAEL was based upon the observation of testicular toxicity and body weight gain suppression at the next higher dose of 0.2 mg/kg-day. Although exposures in the Pant et al. (1995) were for 60-days, this NOAEL was also used for the evaluation of human chronic exposure as a health protective measure. The lowest chronic NOAEL was 0.3 mg/kg-day from a 1-year feeding study in dogs (Toxigenics, 1983) that was based on the observation of testicular degeneration and convulsions at the next higher dose of 0.6 mg/kg-day. Because testicular toxicity was observed in both the subchronic and chronic studies, the health-protective decision was made to use the subchronic NOAEL to evaluate both subchronic and chronic human exposures. While OEHHA agrees with the NOAEL identification in either study, we have concerns regarding the use of a subchronic or chronic regulatory value that exceeds the acute regulatory value.

The critical acute regulatory endpoint of chewing behavior identified in a rat developmental study is considered in the RCD as adverse, and is an effect that suggests the possibility of other significant central effects such as an impact upon "learning or perception." Because of the adverse nature of this effect and the fact that it is a true sign rather than a clinical measurement (e.g. cholinesterase inhibition), OEHHA believes that the seasonal/chronic NOAEL of 0.1 mg/kg-day is not appropriately health protective. Accordingly, OEHHA recommends that the acute regulatory value of 0.01 mg/kg be used to evaluate seasonal and chronic exposures to carbofuran in addition to acute exposures. We are also concerned that the seasonal/chronic regulatory value of 0.1 mg/kg-day as proposed in the RCD is not appropriately protective against known effects in humans as it is only 2.5-fold less than a dose rate which resulted in profound signs and symptoms of

cholinergic toxicity of dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea, and vomiting in a human study. Adoption of the acute regulatory value of 0.01 mg/kg for all exposure durations will protect against these known human effects as well.

2. A default dermal absorption factor of 50% is used in the RCD/EAD for estimating internal dose from dermal exposure to carbofuran. A study by Shah et al. (1987), revealed dermal absorption in rats at 72 hours post-application to be 83% at the lowest dose (28 nmol/cm^2) tested. The same authors (Shah et al., 1981) showed dermal penetration by cabofuran to be faster and more extensive in mice (97.5% dermal absorption at 8 hours). Several reasons for not using this data were presented in the EAD: (1) data was not reported on a wet-weight basis, (2) acetone was used as the vehicle, (3) treated skin was not washed after exposure period, (4) doses were too high (with the exception of the lowest dose in the rat study), (5) treated areas not sufficiently large, and (6) treated skin was covered with perforated blister in the rat study. We find these reasons insufficient to dismiss the data from animal studies, particularly considering that a number of these "reasons" would tend to underestimate absorption rather than overestimate the amount of carbofuran absorbed. Indeed, we find this data more compelling than a "review of data from several chemicals," which was used to derive the default value of 50%. Accordingly, OEHHA proposes that a dermal absorption rate of 83% be used in estimating absorbed carbofuran doses. We also note that a dermal absorption value of 83.4% was apparently applied in an earlier version of the EAD (see page 23 of the RCD where it refers to a dermal absorption value of 83.4% being used to calculate human absorption).

3. A default human inhalation absorption factor of 100% is apparently used in the RCD, as stated on page 94 (and page 9 of the EAD). A default pulmonary absorption in rats of 50% is apparently also assumed in the document (See page 89). It is not clear why two different values are assumed for inhalation absorption. OEHHA suggests that this discrepancy be addressed.

4. OEHHA is concerned that seasonal and chronic airborne exposures for the maximally exposed individual is not evaluated in the RCD/TAC. Individuals residing in rural areas near orchards and other crops to which carbofuran is applied may experience repeated exposures to the relatively high airborne concentrations of this active ingredient following repeated applications. Such exposures may occur several times over the course of a growing season as well as over the course of many growing seasons. Therefore, we recommend that seasonal and chronic exposures and risks be estimated for this hypothetical receptor.

5. Bystander exposure is estimated using the 24-hour time weighted average (TWA) of the measured air concentrations. We are concerned that this is not sufficiently health-

protective. Accordingly, OEHHA recommends that application site exposures be estimated using the highest sub-24-hour air concentration to protect against acute toxicity from short-term spikes in air concentrations.

6. Chronic occupational exposure to carbofuran was not evaluated in the RCD. OEHHA believes it plausible that seasonal exposure could occur over the course of several growing seasons to the same group of workers. We therefore recommend that chronic occupational exposure to carbofuran be evaluated in the RCD. This is a particular concern considering the potentially irreversible testicular toxicity associated with long-term exposure to carbofuran.

7. Occupational exposure to carbofuran was estimated in the RCD/EAD employing three different methodologies, depending upon the exposure type. Handler exposure was estimated using the Pesticide Handler Exposure Database (PHED); exposures for dip/slurry applicators were estimated using dermal absorption equations from U.S. EPA's Risk Assessment Guidance for Superfund (RAGS) and inhalation exposure estimates using U.S. EPA's SWIMODEL program; and exposures of fieldworkers were estimated using dislodgeable foliar residue values and transfer co-efficients. Uncertainties associated with the use of these methods to estimate worker exposures are described in detail in both the RCD and EAD. OEHHA is concerned that no validation of these estimates were performed. Indeed, in the one available handler study (Hussain et al. 1990), many of the measured handler exposures were higher than the mean PHED values used in the assessment. OEHHA recommends that the worker exposures estimated in the RCD be validated before the RCD becomes finalized.

8. Seasonal exposure of drip irrigation mixer/loaders is assumed in the RCD/EAD to occur over the course of two months/year, while chronic exposure to the same individuals is assumed to occur over three months annually. This apparent discrepancy is not discussed in the document(s). OEHHA suggests correcting this apparent inconsistency.

9. MOEs for acute and seasonal occupational exposures to carbofuran were significantly less than 100 for most exposure scenarios and routes of exposure. In fact, for combined dermal and inhalation exposures, most occupational MOEs were less than one, suggesting a significant potential health impact to agricultural workers exposed to carbofuran. Accordingly, because of high potential worker risks, OEHHA recommends that DPR expedite the development of a strategy for mitigation of worker exposure.

10. Estimates of acute and seasonal exposure to carbofuran in ambient air resulted in MOEs greater than 100, suggesting that carbofuran exposure to the general public via the ambient air is not of toxicological concern. Even applying the suggested regulatory value of 0.01 mg/kg to seasonal exposures, MOEs would still be greater than 100. We note that

some of the MOEs for infants are less than 1,000, which is the regulatory benchmark for triggering the listing of carbofuran as a TAC. Acute MOEs for bystanders were less than 100, suggesting the potential for negative human health impacts from application site exposure of the general public to carbofuran. Accordingly, OEHHA recommends that DPR expedite the development of measures to mitigate these exposures.

11. Acute dietary MOEs for essentially all sub-populations evaluated in the RCD were less than 100 and many were less than 10. Tolerance assessment supported this analysis in that MOEs for nearly all commodities were less than 100. Considering these results, OEHHA recommends that DPR engage U.S. EPA in discussions aimed at reviewing the current federal tolerance to carbofuran on all products.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

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References

Pant N, Prased AK, Srivastava SC, Shankar R and Srivastava SP (1995). Effect of oral administration of carbofuran on male reproductive system of rat. Human & Experimental Toxicol. 14:889-894.

Shah PV, Monroe RJ and Guthrie FE (1981). Comparative rates of dermal penetration in mince. Toxicol. Appl. Pharmacol. 59:414-423.

Shah PV, Fisher HL, Month NJ, Sumler MR, and Hall LL (1987). Dermal penetration of carbofuran in young and adult Fischer 344 rats. J. Toxicol. Environ. Health 22:207-223.

WARF (1978). Teratopgeniocity of carbofuran in rats. WARF Institute, Inc., Madison, WI. No study date provided. WARF #T-730. DPR Volume #254-137, Record #87711.

Jayutunga YNA, Dangalle CD, and Ratnasooriya WD (1998). Hazardous effects of carbofuran on pregnancy outcome of rats. Medical Science Research 26:679-683.

FMC (1976). Oral toxicity study (human) [carbofuran] (summary only). Quincy Research Center. ACT 152.03. DPR Volume #254-029, Record #46697.

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DATE: March 29, 2006

SUBJECT: CARBOFURAN – RESPONSE TO OEHHA'S COMMENTS ON DPR'S RISK CHARACTERIZATION AND EXPOSURE ASSESSMENT DOCUMENTS

Enclosed is the Department of Pesticide Regulation's response to the Office of Environmental Health Hazard Assessment's comments on DPR's risk characterization document (RCD) and exposure assessment document (EAD) for the pesticide active ingredient, carbofuran.

If you have questions concerning the draft RCD, please contact Dr. Gary Patterson at (916) 445-4233. If you have questions concerning the draft EAD, please contact Mr. Charles Andrews at (916) 445-4222.

Enclosures

cc: Dr. George Alexeeff (e-copy w/enclosures)
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TO: Joyce Gee, Ph.D., Senior Toxicologist, Health Assessment Group, Medical Toxicology Branch
Gary T. Patterson, Ph.D., Supervising Toxicologist, Medical Toxicology Branch

FROM: Andrew L. Rubin, Ph.D., D.A.B.T., Staff Toxicologist, Health Assessment Group, Medical Toxicology Branch

DATE: January 23, 2006

SUBJECT: Responses to OEHHA's 7.07.05 comments on DPR's 3.01.05 draft carbofuran RCD

OEHHA comments and DPR responses are numbered according to the system in OEHHA's memo.

OEHHA comment #1: OEHHA agreed with DPR's designation of the critical acute LED_{05} value at 0.01 mg/kg, based on abnormal chewing motions in rats observed at 0.1 mg/kg. Because this was the lowest dose tested, a benchmark dose estimation of the LED was triggered. However, in contrast to the draft RCD, OEHHA recommended that the acute value also be used to evaluate seasonal and annual risk, citing a concern that the seasonal/chronic NOAEL in the RCD was not appropriately health protective. This judgment was based on the observation that the relevant critical subchronic and chronic endpoint values identified in the RCD (0.1 mg/kg/day in both cases, based on testicular damage and weight decrements in a 60-day rat study) were *higher* than the acute value. Thus protection against seasonal/annual effects would not necessarily protect humans from the acute effect, the adverse nature of which is undisputed. OEHHA also suggested "that the seasonal/chronic regulatory value of 0.1 mg/kg-day as proposed in the RCD is not appropriately protective against known effects in humans as it is only 2.5-fold less than a dose rate which resulted in profound signs and symptoms of cholinergic toxicity of dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea, and vomiting in a human study" (pp. 3-4).

DPR response: DPR recognizes that designation of the critical subchronic and chronic NOELs at a higher dose than the parallel acute value is unusual. In most risk assessment cases, longer-term regulatory values are lower than their shorter-term counterparts, reflecting the toxicologic principle that longer exposures require lower doses to elicit similar responses. In the present case, however, it is important to recognize that the relevant endpoints, abnormal chewing behavior in the acute case and testicular damage in the subchronic and chronic cases, are different. Explicit recognition of this in the draft RCD with respect to the designation of critical regulatory values in the draft RCD does not compromise human health. Protection against untoward acute effects at the lower dose level guarantees protection against subchronic/chronic effects that may occur at higher doses.

The draft RCD chose to assess seasonal and annual risks using toxicity study lengths that were closer approximations to seasonal and annual human exposure than the critical acute study. Acute cholinergic effects (*eg.*, abnormal chewing motions) would likely disappear upon repeated

exposure as the animals adapt to the constant presence of a cholinergic stressor (and were, in any case, not seen in the critical subchronic study). Therefore, use of the subchronic endpoint avoided use of an acute sign that was, in all likelihood, irrelevant to the exposure length. Viewed in another way, a serious endpoint (testicular damage) that *was* relevant to seasonal and annual exposures was explicitly recognized in the subchronic/chronic critical NOEL designation.

Nonetheless, in recognition of OEHHA's suggestion, the following wording will be added at the end of section V.2.a. (Risk Appraisal, subchronic toxicity): "Setting the subchronic (and chronic) critical NOEL one order of magnitude higher than the critical acute level, while unusual in a risk assessment, is not likely to compromise human health. Protection against untoward acute effects at the lower dose level would ensure protection against subchronic / chronic effects, regardless of their nature, occurring at higher doses."

OEHHA comment #2: OEHHA is reluctant to use a default dermal absorption value of 50% in view of higher values reported by Shah *et al.* (1981 and 1987).

DPR response: Designation of an appropriate dermal absorption value falls within the provenance of the Worker Health and Safety Branch, which produced the Exposure Assessment Document (DPR, 2006). The revised RCD continues to use the default value of 50%. Further details are provided in the parallel WH&S memo from Dr. Sheryl Beauvais to Dr. Joseph Frank, dated Dec. 14, 2005.

OEHHA comment #3: An inconsistency in the inhalation absorption value used to calculate inhalation exposure was pointed out. While a value of 100% was used for the majority of the RCD and EAD (including all of the calculated inhalation doses), a theoretical calculation presented on page 89 of the draft RCD used a value of 50%.

DPR response: The calculation on page 89 has been amended such that 100% inhalation absorption is assumed. The correction, which resulted in a two-fold increase in the estimated LD50 based on this theoretical calculation, does not change any of the resultant conclusions.

OEHHA comment #4: OEHHA is concerned that the draft RCD did not evaluate potential seasonal and chronic inhalation risks to the maximally exposed individual and recommends that these scenarios be addressed.

DPR response: The draft RCD evaluated potential seasonal exposures under ambient scenarios, but did not evaluate annual (chronic) exposures. Neither seasonal nor annual exposures were evaluated under application site scenarios. Upon review of the use data, and in light of OEHHA's comment, DPR now concludes that there is a potential for annual exposure

under ambient conditions. The revised RCD now contains an annual exposure estimate (as provided in the Exposure Assessment Document [DPR, 2006]) and an evaluation of chronic risk under that condition.

The draft RCD only evaluated potential acute exposures under application site scenarios. This was based on the conviction that application site air levels were expected to approach ambient levels within a few days of the application. As this remains the reasoning in the Exposure Assessment Document, application site risk continues only to be estimated under acute exposure conditions.

Further details are provided in the parallel WH&S memo from Dr. Sheryl Beauvais to Dr. Joseph Frank, dated Dec. 14, 2005.

OEHHA comment #5: OEHHA is concerned that the 24-hr time weighted average (TWA) estimation of acute application site exposure is not sufficiently health protective because it does not take into account the highest sub-24-hr measurements.

DPR response: DPR agrees with OEHHA's concern, as the 24-hr TWA does indeed average out sub-24-hr air concentration measurements. Accordingly, the revised RCD contains, in addition to the 24-hr TWA estimates, 1-hr maximum exposure estimates for application site scenarios. Details are provided in the parallel WH&S memo (Beauvais to Frank, Dec. 14, 2005).

OEHHA comment #6: OEHHA recommends that the risks from chronic exposure should be evaluated under occupational scenarios, particularly in view of the potential for carbofuran-induced testicular toxicity.

DPR response: Review of the exposure data indicates that OEHHA's recommendation is well-founded in most cases. The revised RCD now contains annual (chronic) risk estimates for handlers, fieldworkers and ambient-exposed bystanders. Only application site scenarios are restricted to acute risk estimations (see response to OEHHA comment #4).

OEHHA comment #7: OEHHA recommends that the exposure estimates, which were arrived at by different methodologies, be validated before finalization of the RCD.

DPR response: This question is more apropos to the Worker Health and Safety Branch, which produced the Exposure Assessment Document (DPR, 2006). Details are provided in the parallel WH&S memo (Beauvais to Frank, Dec. 14, 2005).

OEHHA comment #8: Drip irrigation mixer/loader seasonal *vs.* annual calculations contain an apparent inconsistency.

DPR response: See parallel WH&S memo (Beauvais to Frank, Dec. 14, 2005).

OEHHA comment #9: OEHHA recommends development of a mitigation strategy for occupational exposures.

DPR response: See parallel WH&S memo (Beauvais to Frank, Dec. 14, 2005).

OEHHA comment #10: OEHHA recommends development of a mitigation strategy for some ambient exposures and for application site exposures.

DPR response: See parallel WH&S memo (Beauvais to Frank, Dec. 14, 2005).

OEHHA comment #11: OEHHA recommends opening discussions with USEPA to revisit current tolerances in view of the low MOEs emerging from the tolerance assessment.

DPR response: USEPA has sole responsibility for setting tolerances. As it will receive a copy of the revised carbofuran RCD, it should be aware of the very low MOE values reported in the DPR document. Adjustment of current tolerances could conceivably result from their knowledge of the document's contents.

References

DPR. 2006. Estimation of Exposure of Persons in California to Pesticide Products that Contain Carbofuran. Document #HS-1803 (authors: S. Beauvais and J. Johnson), Worker Health and Safety Branch, Dept. of Pesticide Regulation, Cal-EPA. January 23, 2006

Shah, P.V., R.J. Monroe and F.E. Guthrie. 1981. Comparative rates of dermal penetration of insecticides in mice. *Toxicol. Appl. Pharmacol*. **59**:414-423

Shah, P.V., H.L. Fisher, N.J. Month, M.R. Sumler and L.L. Hall. 1987. Dermal penetration of carbofuran in young and adult Fischer 344 rats. *J. Toxicol. Environ. Health* **22**:207-223

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DATE: December 14, 2005

SUBJECT: RESPONSE TO OEHHA COMMENTS ON DRAFT CARBOFURAN RISK CHARACTERIZATION DOCUMENT

The draft Risk Characterization Document (RCD) for carbofuran was distributed for external peer review June 2, 2005 (Rubin, 2005). The Office of Environmental Health Hazard Assessment (OEHHA) reviewed Rubin (2005) and sent comments in a memo dated July 7, 2005. The review was greatly appreciated, and as mentioned below resulted in at least one important change to estimates in the RCD.

This memorandum responds to comments 2, 4, 5, and 7 through 10 in that review, which address the exposure assessment prepared by the Worker Health and Safety (WHS) Branch of the Department of Pesticide Regulation (DPR). The Medical Toxicology (MT) Branch will respond separately to comments 1, 3, 6, and 11, which address decisions made by MT.

Comment 2: Dermal absorption factor should be 83%, not 50%.

This comment recommended that DPR use 83% as the dermal absorption factor, based on data from Shaw *et al.* (1987). As noted in the comment, the rationale for choosing the 50% default over a value of 83% was not compellingly stated. However, I believe that 50% is the best choice, and I will attempt to explain it more convincingly.

The dermal absorption of 83% was estimated at 72 hours. This was the only time-point available for the low dose. Initially, WHS considered using this value, because other studies have shown that a higher dermal absorption may often occur with lower dose (Thongsinthusak *et al*., 1999). However, consideration of all data presented by Shah *et al*. (1987), and summarized below in Table 1 and Table 2, suggests that the 83% value is anomalously high and unlikely to be predictive of dermal penetration of carbofuran in humans.

Shah *et al.* (1987) determined dermal penetration of carbofuran dissolved in acetone in groups of 3 adult (82-day old) and 3 young (33-day old) rats. Dermal penetration was reported as the mean $\pm$ SD of each 3-rat group. This study had two types of *in vivo* experiments, the results of which are summarized in Tables 1 and 2.

Table 1. Dermal penetration of several doses of carbofuran at 72 hours [a]

Dose (nmol/cm^2)	% Absorbed (adults)	% Absorbed (young)
28	83.4 ± 0.8	24.5 ± 8.5
285	13.0 ± 1.1	36.3 ± 2.5
535	8.3 ± 0.2	9.2 ± 0.9
2,680	6.0 ± 0.2	3.7 ± 0.2

[a] Adapted from Table 3 of Shaw *et al.* (1987).

Table 2. Dermal penetration of a single dose of carbofuran (285 nmol/cm^2) at multiple timepoints (6, 24, 48, 72, and 120 hours) [a]

Hour	% Absorbed (adults)	% Absorbed (young)
6	2.1 ± 0.2	5.2 ± 0.6
24	6.2 ± 1.3	26.2 ± 1.9
48	7.4 ± 0.2	28.4 ± 2.9
72	13.0 ± 1.1	36.3 ± 2.5
120	17.8 ± 2.7	43.0 ± 5.8

[a] Adapted from Table 1 of Shaw *et al.* (1987).

This study, as well as the dermal absorption of carbofuran in mice reported by Shah *et al.* (1981), are anticipated to overestimate dermal absorption in humans. Both studies used acetone as a vehicle. Acetone has been shown to substantially increase dermal absorption of several compounds, including pesticides (Moody *et al.*, 1992; Baynes *et al*., 1997; Baynes and Riviere, 1998; Stinchcomb *et al.*, 1999; Tsai *et al.*, 2001). Organic solvents, including acetone, can damage the skin barrier properties, artificially increasing dermal penetration (Scheuplein and Ross, 1970; Fartasch, 1997; Williams and Barry, 2004). For this reason, U.S. EPA (1998) recommends that the vehicle used in dermal penetration studies should be the same as that "under which field exposure occurs," and states that organic solvents "must not be used."

The highest dermal absorption of carbofuran, 94.7%, was reported in mice (Shah *et al.*, 1981). Comparison of the four other pesticides tested at comparably low doses in these two studies in both mice (at a dose of 20 μg/cm^2) and rats (at doses ranging 2 – 37 μg/cm^2) showed that in each case absorption was lower in rats following 72 hours of exposure than in mice following 8 – 48 hours exposure (Shah *et al*., 1981; Shah *et al*., 1987a). Furthermore, dermal absorption of all fourteen pesticides tested in mice by Shah *et al*. (1981) exceeded 65% at 8 hours, suggesting that all of these results were higher than would normally be anticipated. For four of the pesticides tested by Shah *et al*. (1981) in mice, Ross *et al.* (2001) reported human dermal absorption of 10% or less. In other studies involving other pesticides, mice also showed higher dermal absorption than rats or humans (U.S. EPA, 1992; Baynes et al., 1997). Because of the use of

mice, but mainly due to the use of acetone as a vehicle, the study by Shah *et al.* (1981) was considered unacceptable.

The highest mean dermal absorption of carbofuran reported in rats was 83% (Shah *et al*., 1987b). Table 1 and Table 2 shows this result to be more than double any other result in the study. In contrast to the pattern seen with other doses, this high result occurred in adults rather than young rats. Because results were presented on a wet-weight basis, and no organ wet weights were given, these discrepancies could not be investigated, nor were they explained by Shah *et al*. (1987b). With the exception of this one result, all dermal absorption results for all dose levels and exposure intervals were less than 40%.

In addition to the use of acetone as a vehicle, there were other ways in which the study conducted by Shah *et al*. (1987b) did not conform to accepted methods (Thongsinthusak, 1994; U.S. EPA, 1998a). The treated skin was covered with a perforated plastic blister, which is possibly an occlusive cover. The treated skin was not washed off after the exposure period. Doses tested for durations approximating a workday (8 hours) were too high (Thongsinthusak *et al*., 1999). Treated areas measured 2.8 cm^2 for the juveniles and 5.6 cm^2 for the adults, rather than the recommended 10 cm^2. While each of these factors might be expected to result in underestimation of dermal absorption, the use of acetone as a vehicle may have mitigated the effect. Overall, this study was considered unacceptable.

When no acceptable data are available for dermal absorption, DPR uses a default value of 50% (Donahue, 1996). This default value is based on a review of data from studies using forty pesticides, twenty-six of which were documented in Thongsinthusak *et al*. (1993). The mean $\pm$ standard deviation dermal absorption in rats of these 40 pesticides was 19 $\pm$ 14% (Donahue, 1996). Dermal absorption in rats would furthermore be anticipated to overestimate dermal absorption in humans. Ross *et al.* (2001) compared in vivo dermal absorption of fourteen pesticides in rats and humans. Dermal absorption in rats ranged 3 – 95% (mean $\pm$ standard deviation: 38 $\pm$ 26), while dermal absorption in humans ranged 1 – 43% (mean $\pm$ standard deviation: 10 $\pm$ 11). DPR is not aware of any properly-conducted study that demonstrated dermal absorption greater than 50% in humans, and DPR considers 50% dermal absorption to be a health-protective default. The data available for carbofuran do not support use of a higher value for dermal absorption.

Comment 4: Seasonal and chronic exposures should be estimated for bystanders.

This comment recommended that DPR estimate seasonal and chronic exposures for individuals living in areas where multiple treatments per growing season could occur. In the draft RCD, DPR provided a 24-hour exposure estimate. Application site air monitoring suggests that the off-site concentration decreases quickly. Monitoring by ARB (1994) showed that for three of the four stations, one day post-application carbofuran concentrations were in the range of 0.035 to

0.12 μg/m^3. Mean carbofuran concentrations on which seasonal and chronic ambient air exposure estimates are based were in the range of 0.0006 to 0.033 μg/m^3. Even in the case of multiple applications in an area individuals are not anticipated to be exposed to elevated concentrations for more than a day. The exposure assessment document states that exposures are anticipated to reach ambient levels within a few days.

The Furadan 4f product label and the three Special Local Needs registrations all specify the maximum number of applications allowed per growing season for each crop. Only one application is allowed per growing season on the following crops: alfalfa, cotton, sunflowers, and tobacco. A maximum of two applications per growing season are allowed on artichokes, field corn, sweet corn, popcorn, potatoes, wheat, oats, barley, soybeans, and sugarcane. Grapes may be sprayed a maximum of three times per growing season. With limitations on numbers of applications to each crop, even an individual adjacent to more than one application site would at most experience elevated airborne carbofuran concentrations for a few days each year.

DPR defines acute exposure as exposures lasting from less than a day to short-term intervals up to one week. The acute absorbed daily dosage (ADD) reported in the draft RCD, based on a 24-hour time-weighted average, is considered adequate for bystander exposures.

Comment 5: Bystander exposure estimates should be based on the highest measured sub-24-hour air concentration.

This comment recommended that DPR estimate bystander exposure based on an exposure interval less than 24 hours, as carbofuran has toxic effects at shorter intervals. WHS recognizes the validity of this suggestion, and in response will use the highest concentration measured by ARB (1994) to estimate a one-hour bystander exposure. The highest concentration reported by ARB (1994) was measured during a one-hour sample that spanned the application, 0.66 μg/m^3. However, in ARB (1994) carbofuran was applied at a rate (0.3 lb AI/acre) that was below the maximum application rate allowed on alfalfa (1.0 lb AI/acre). Bystanders near a field receiving the maximum application rate would be anticipated to be exposed to higher concentrations than measured by ARB (1994). The concentration used to estimate exposure was therefore adjusted (multiplied by 1.0/0.3 = 3.3) to 2.2 μg/m^3.

In addition, the inhalation rates for 1-hour absorbed dose estimates were calculated from values reported in Andrews and Patterson (2000), assuming heavy activity and dividing by the median body weight for males and females. Hourly inhalation rates for heavy activity are 1.9 m^3/hr for infants and 3.2 m^3/hr for adults. The 1-hour absorbed dose was 0.000550 mg/kg/hr for infants and 0.000099 mg/kg/hr for adults.

The bystander exposure estimate based on the 24-hour time-weighted average carbofuran concentration and inhalation rates considered typical for daily activity (Andrews and Patterson, 2000) will be retained for exposure durations of more than an hour and up to a week.

Comment 7: Worker exposure estimates should be validated before RCD is finalized.

This comment recommended that WHS not use exposure estimates unless such estimates had been validated first. In particular, OEHHA noted the fact that the one occupational exposure monitoring study available reported higher exposures than those estimated using the Pesticide Handler Exposure Database (PHED, 1995). Only one study was available in which exposure monitoring was done with handlers of carbofuran. Hussain *et al*. (1990) monitored four mixer/loader/applicators (M/L/As) and two applicators. This study was considered unacceptable for two reasons, the small sample size and the fact that results were not reported in an activity-specific way.

Two factors are considered to explain the higher exposure estimates reported by Hussain *et al.* (1990). The first is that four of the six handlers performed mixing/loading as well as applications (i.e., they were M/L/A). The arithmetic mean total exposure rate reported by Hussain *et al.* (1990) was 574.4 µg AI/lb handled. The six handlers (two applicators and four M/L/As) monitored by Hussain *et al.* (1990) had the following six total exposure estimates: 33.8, 42.6, 123.6, 223.6, 437.2, and 2,585.6 µg AI/lb handled (note that five of the six handlers monitored by Hussain *et al*. (1990) had exposures below the arithmetic mean). In Table 5 in the exposure assessment document, the PHED mean estimates used in calculating Acute ADD for groundboom mixer/loaders and applicators are 77.8 and 107 µg/lb handled, respectively. If the two lowest results reported by Hussain *et al.* (1990) are for the two applicators, then PHED overestimated the applicator exposure by about three-fold (107 µg AI/lb handled vs. 33.8 and 42.6 µg AI/lb handled). However, insufficient information was provided by Hussain *et al.* (1990) to assign exposure results to handler activities in that study.

A second reason for the discrepancy between exposure monitoring results reported by Hussein *et al.* (1990) and PHED-based exposure estimates is that workers monitored in the study wore different clothing than is required by the existing product label and California regulations. The greatest contribution to the exposures reported by Hussain *et al.* (1990) was hand and wrist exposures. Hussain *et al.* (1990) found that on average hands and wrists accounted for 87.2% of total exposure (for the individual with the greatest estimated exposure, hands and wrists accounted for 96.9% of the total). Individuals monitored by Hussain *et al.* (1990) did not wear gloves during the applications. As the product label requires chemical-resistant gloves for all handler activities, PHED-based estimates incorporated an assumption that workers would wear gloves.

DPR recognizes that validation of exposure estimates with high-quality exposure monitoring data is preferred whenever feasible. However, these data are expensive to acquire. PHED has been instrumental in the regulatory process of identifying potential exposure issues, and it often provides the best exposure monitoring data available. But because of its limitations, which were discussed in the exposure assessment document, the regulated community is spending a significant amount of time and money to replace that database with a more scientifically robust one. New data have been submitted for some scenarios already from well-conducted studies. Meanwhile, DPR will continue to make decisions based on the best available data.

Comment 8: The difference in durations between seasonal and annual exposure estimates should be clarified.

This will be done.

Comments 9 and 10: Mitigation.

The low MOEs have already been noticed and discussed within DPR. As noted in this comment, RCDs do not include mitigation measures by design. This is appropriate, as the risk assessment must be finalized before mitigation measures can be addressed. DPR feels that the RCD process is the proper way to identify needed mitigation measures.

References

Air Resources Board (ARB). 1994. Ambient Air Monitoring for Carbofuran in Imperial County During Spring 1993, After an Application to an Alfalfa Field. Test Report No. C93-013A, Report Date March 24, 1994; Sacramento, CA: Toxic Air Contaminant Identification Branch, Air Resources Board, California Environmental Protection Agency.

Andrews, C. and Patterson, G. 2000. Interim Guidance for Selecting Default Inhalation Rates for Children and Adults. HSM-00010. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Baynes, R.E., Halling, K.B. and Riviere, J.E. 1997. The influence of diethyl-m-toluamide (DEET) on the percutaneous absorption of permethrin and carbaryl. Toxicology and Applied Pharmacology 144:332-339.

Baynes, R.E. and Riviere, J.E. 1998. Influence of inert ingredients in pesticide formulations on dermal absorption of carbaryl. American Journal of Veterinary Research 59:168-175.

Donahue, J. 1996. Revised Policy on Dermal Absorption Default for Pesticides. Memo No. HSM-96005, dated July 5. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

Fartasch, M. 1997. Ultrastructure of the epidermal barrier after irritation. Microscopy Research and Technique 37:193-199.

Hussain, M., Yoshida, K., Atiemo, M. and Johnston, D. 1990. Occupational exposure of grain farmers to carbofuran. Archives of Environmental Contamination and Toxicology 19:197-204.

Moody, R.P., Wester, R.C., Melendres, J.L. and Maibach, H.I. 1992. Dermal absorption of the phenoxy herbicide 2,4-D dimethylamine in humans: effect of DEET and anatomic site. Journal of Toxicology and Environmental Health 136:241-250.

PHED. 1995. The Pesticide Handlers Exposure Database, Version 1.1. Prepared for the PHED Task Force representing Health and Welfare Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association; prepared by Versar, Inc., 6850 Versar Center, Springfield, VA 22151.

Ross, J.H., Driver, J.H., Cochran, R.C., Thongsinthusak, T. and Krieger, R.I. 2001. Could pesticide toxicology studies be more relevant to occupational exposure risk assessment? Annals of Occupational Hygiene 45(Supplement 1):S5-S17.

Rubin, A.L. 2005. Risk Characterization Document: Carbofuran. Final Draft, dated March 1, 2005. Sacramento, CA: Medical Toxicology Branch, Department of Pesticide Regulation.

Scheuplein, R.J. and Ross, L.W. 1970. Effects of surfactants and solvents on the permeability of epidermis. Journal of Society of Cosmetic Chemists 21:853–873.

Shah, P.V., Monroe, R.J. and Guthrie, F.E. 1981. Comparative rates of dermal penetration of insecticides in mice. Toxicology and Applied Pharmacology 59:414-423.

Shah, P.V., Fisher, H.L., Month, N.J., Sumler, M.R. and Hall, L.L. 1987. Dermal penetration of carbofuran in young and adult Fisher 344 rats. Journal of Toxicology and Environmental Health 22:207-223.

Stinchcomb, A.L., Pirot, F., Touraille, G.D., Bunge, A.L. and Guy, R.H. 1999. Chemical uptake into human stratum corneum in vivo from volatile and non-volatile solvents. Pharmaceutical Research 16:1288-1293.

Thongsinthusak, T., Ross, J., Sanborn, J. and Wang, R. 1993. Dermal Absorption of Pesticides in Animals and Humans. Report No. HS-1676. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Thongsinthusak, T., Ross, J.H. and Dong, M.H. 1999. Significance of Dermal Dose Levels in Dermal Absorption Studies of Pesticides. Report No. HS-1801. Sacramento, CA: California Department of Pesticide Regulation, Worker Health and Safety Branch.

Tsai, J.C., Sheu, H.M., Hung, P.L. and Cheng, C.L. 2001. Effect of barrier disruption by acetone treatment on the permeability of compounds with various lipophilicities: implications for the permeability of compromised skin. Journal of Pharmaceutical Sciences 90:1242-1254.

U.S. EPA. 1992. Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/011B. Washington, DC: Office of Health and Environmental Assessment, United States Environmental Protection Agency.

U.S. EPA. 1998. Health Effects Test Guidelines. OPPTS 870.7600: Dermal Penetration. EPA 712-C-98-350. Washington, DC: Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency.

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